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RADIATION THERAPY OF NON-HODGKIN'S LYMPHOMA STAGES I AND II

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Historically, 'localized' disease in patients with malignant lymphoma has included stages I and II according to the Ann Arbor staging system (CARBONE et coll. 1971). These stages have by tradition been treated with irradiation alone. Stages III and IV have been assumed to represent 'generalized' disease, chemotherapy usually being the treatment of choice. In non-Hodgkin's lymphoma (NHL) the 5-year survival rate achieved by irradiation as the primary treatment has ranged from 33 to 59 per cent for patients whose disease has been classified as stages I and II (JONES et coll. 1973, PECKHAM et coll. 1975, BUSH et coll. 1977, CHEN et coll. 1979, SWEET et coll. 1981). In most reports stages I and II have not been separated, but some reports indicate that a great difference in survival may exist between these two stages, especially among patients with more malignant histopathologic appearances (CHEN et coll., SWEET et coll.). The question whether patients in stage II have a localized disease or not, and whether this group of patients should primarily be treated with irradiation alone does not seem to have been unequivocally solved. As part of a retrospective analysis of NHL, using the Kiel classification (GLIMELIUS & SUNDSTRÖM 1982), it was considered of value to compare in detail the long-term survival in a series of patients with NHL in clinical stages I and II, since these patients were uniformly irradiated throughout the period in question.

Material and Methods

The series comprised 147 previously untreated patients (83 males, 64 females, mean age 62 years, range 17–92) with microscopically proven NHL. Their disease was classified as either stage I (99 cases) or stage II (48 cases), and they were primarily given radiation therapy alone. All patients had been referred to this hospital between January 1970 and December 1980. During this period the total number of proven NHL in stages I and II was 171 (116 in stage I, 55 in stage II). Among the remaining 24 patients (17 in stage I, 7 in stage II), who had not been treated exclusively with irradiation, 12 (9 in stage I, 3 in stage II) had received adjuvant chemotherapy and 2 (1 each in stage I and II) had been treated with chemotherapy alone; 10 (7 in stage I, 3 in stage II) had only been operated upon.

Histopathology. All specimens were examined by one of the authors (CS) and classified according to the Kiel system (GÉRARD-MARCHANT et coll. 1974). High-grade malignancy comprises centroblastic, lymphoblastic and immunoblastic lymphomas, while low-grade malignancy comprises lymphocytic, immunocytic, centrocytic and centroblastic centrocytic lymphomas.

Clinical records. The patients were clinically staged in accordance with the 1971 Ann Arbor criteria (CARBONE et coll.). Waldeyer's ring and the spleen were considered as lymphatic sites. Routine examinations included chest radiography, bone marrow smear and clot section. A detailed extranodal examination was performed. The following examinations were optional (the figures in parentheses showing the number of patients in the two stages):

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bone marrow biopsy (25 in I, 9 in II) lymphangiography (15 in I, 9 in II), computed tomography of the abdomen (27 in I, 8 in II), ultrasound of the abdomen (22 in I, 6 in II) and scintigraphy of the liver and spleen (63 in I, 41 in II). Staging laparatomy was not performed, but in 27 cases (19 in I, 8 in II) the primary diagnosis was made after an explorative laparatomy. A complete clinical staging procedure, including at least one of the intraabdominal examinations mentioned, except scintigraphy, was performed in 64 per cent of the patients in stage I and 66 per cent in stage II. Bulky disease was defined as a single tumour site measuring more than 10 cm in diameter. All patients were followed from admission to death, or to the end of the observation period, i.e. October 1981. The observation time was at least 12 months in all cases. No single patient was lost to follow-up. Disease-free survival was defined as the time period between the date of diagnosis and relapse.

Treatment. The radiation therapy was given with an 8 MeV linear accelerator. The daily tumour doses were 1.5 to 2.0 Gy, giving a total dose of approximately 40 Gy (range 24–54) including all areas of known disease plus a margin of 5 cm, and usually including the neighbouring lymph node station. At relapse most of the patients received chemotherapy according to the principles followed for stages III and IV. The chemotherapy varied considerably during the period, particularly during the first five years when some patients were treated exclusively with a single drug. After 1975 most of the patients with more malignant histopathologic type received MEV (methotrexate, cyclophosphamide, vincristine) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and patients with less malignant type received COP (cyclophosphamide, vincristine, prednisone) or Prednimustine (a chlorambucil ester of prednisolone, AB Leo, Helsingborg, Sweden).

Statistical methods. The survival curves were produced and the statistical significance tested (log-rank test) as described by PETO et coll. (1977). Patients who died from intercurrent diseases were not included in the population at risk provided they were in complete clinical remission before death; if not, they were regarded as having died of malignant lymphoma.

Results

The patient characteristics according to stage and histopathology are summarized in Table 1 and the location of the extranodal lymphomas appears in Table 2. No case of lymphocytic lymphoma in stages I or II was included in the series. Bulky disease was found in 18 patients (14 in stage I, 4 in stage II). A history of B-symptoms was found in 8 patients (4 each in stages I and II). Of the patients in stage II, 36 (75%) had disease limited to two contiguous regions while 12 patients (25%) had disease outside contiguous regions. The abdomen was involved in 19 patients (14 in stage I, 5 in stage II). Analysis of survival curves for the 147 patients (99 in stage I, 48 in stage II) given radiation therapy alone (Fig. 1) revealed that patients initially in stage II had a significantly shorter survival than those in stage I ($p<0.001$). Complete remission after irradiation was obtained in 92 (93%) of the 99 patients in stage I and in 36 (75%) of the 48 in stage II. The reasons for failure in relation to microscopic type appear in Table 3. Failure of local control occurred in 5 patients (5%) in stage I and in 6 (12%) in stage

Table 1

Distribution of stage and histopathologic subgroups according to the Kiel classification

	Stage I	Stage II
Unclassified	8	4
Immunocytic	21	5
Centrocytic	0	2
Centroblastic/centrocytic	31	13
Centroblastic	23	10
Lymphoblastic	8	3
Immunoblastic	8	11
Total	99	48

Table 2

Sites of extranodal involvement at presentation

Site	Stage I	Stage II
Stomach	8	3
Skin	8	1
Thyroid	6	4
Intestine	6	4
Head and neck	7	4
Eye and orbit	2	1
Others	8	
Total	45	17

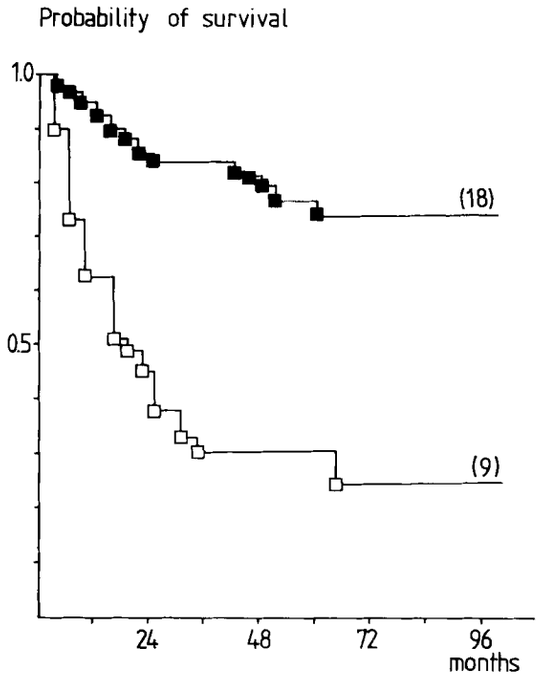

Fig. 1. Actuarial survival of patients in stage I (■ n=99) and in stage II (□ n=48) primarily irradiated. The number of patients surviving after an observation time of more than 96 months is given in parentheses.

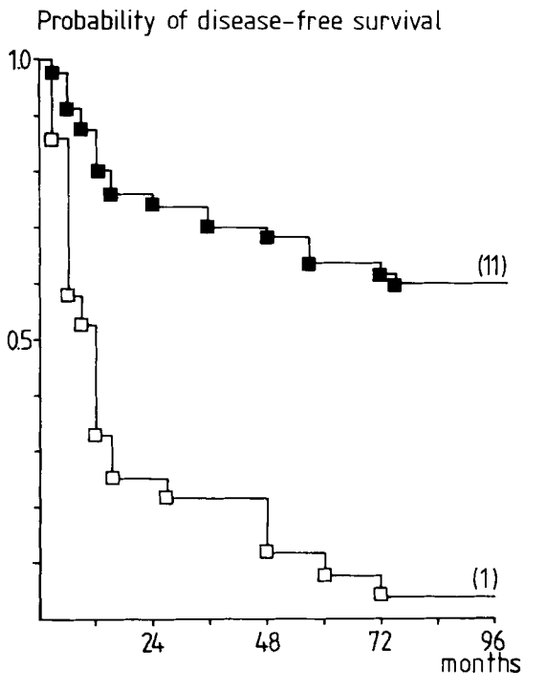

Fig. 2. Disease-free survival of patients in stage I (■ n=92) and stage II (□ n=36) irradiated to complete clinical remission. The number of patients surviving after an observation time of more than 96 months is given in parentheses.

II. Systemic spread during irradiation occurred in 2 patients (2%) in stage I and in 6 (12%) in stage II. Patients with high-grade malignancies accounted for 13 (68%) of the 19 failures. In only one patient with a low-grade malignant lymphoma local control was not achieved by radiation therapy (42 Gy).

A major difference was noted in the disease-free survival between the 92 patients in stage I and the 36 patients in stage II treated to complete remission (Fig. 2). Patients in stage I had a 5-year disease-free survival of 60 per cent whereas the corresponding figure for stage II patients was only 8 per cent. No

Table 3

Reason for immediate failure of radiation therapy

	High-grade			Low-grade			Unclassified	Total
	LB	IB	CB	CC	CB/CC	IC		
Failure of local control								
Stage I		2	2		1			5
Stage II		1	3			1	1	6
Systemic spread during irradiation								
Stage I		1	1					2
Stage II	1	1	1	1	1	1		6
Total		13			5		1	19

IC = immunocytic, CC = centrocytic, CB/CC = centroblastic/centrocytic, CB = centroblastic, LB = lymphoblastic, IB = immunoblastic.

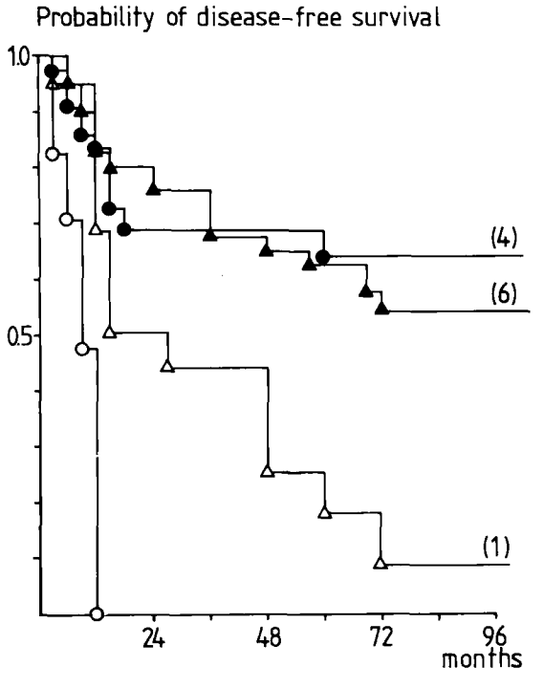

Fig. 3. Disease-free survival of patients in stages I and II with low-grade and high-grade malignancy irradiated to complete clinical remission. Low-grade malignancy: Stage I (▲ n=51) and stage II (△ n=16). High-grade malignancy: Stage I (● n=32) and stage II (○ n=17). The number of patients surviving after an observation time of more than 96 months is given in parentheses.

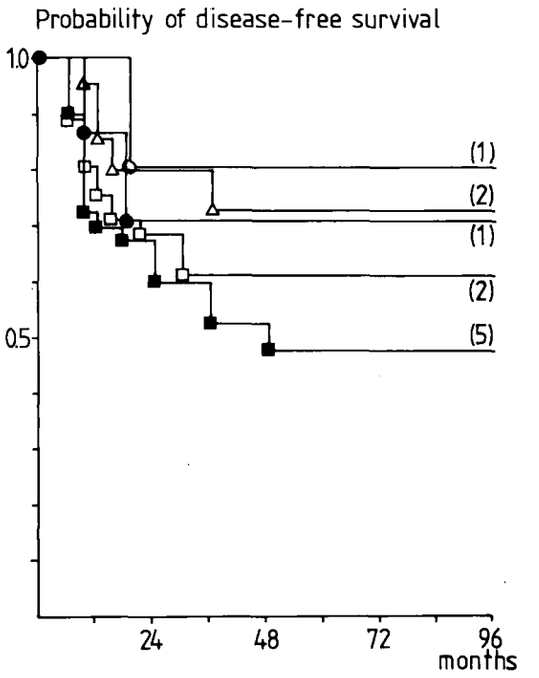

Fig. 4. Actuarial disease-free survival of patients in stage I with different histopathologic type. Lymphoblastic (● n=8), centroblastic (□ n=20), immunoblastic (○ n=5), immunocytic (△ n=21), and centroblastic/centrocytic (▮ n=30). The number of patients surviving after an observation time of more than 96 months is given in parentheses.

statistically significant difference in disease-free survival was found between patients with low-grade and those with high-grade malignancy, either in stage I or in stage II (Fig. 3). The patients with low-grade malignancy stage I had slightly later relapses than those with high-grade malignancy. A subdivision of the patients in stage I according to histopathologic type appears in Fig. 4.

Patients in stage II had a poor prognosis. Actually, only 2 patients were found to be free from disease at the final follow-up. Both of these patients belonged to the group of low-grade malignancy, one with follicular centroblastic/centrocytic lymphoma (followed 132 months) and one with an immunocytic lymphoma (50 months). The poor prognosis following radiation therapy among patients in stage II was present even after exclusion of patients who were not completely staged. When the corresponding cases were excluded also in stage I, the disease-free survival was actually even better than when all stage I cases were included. Following irradiation, 70 per cent of the patients who were completely staged remained disease-free.

The prognosis for patients with extranodal involvement at presentation was similar to that for patients with only nodal involvement.

Discussion

In this retrospective analysis of a 10-year material of localized NHL given radiation therapy alone, patients in stage II had a very poor prognosis, whereas those in stage I had a considerably better prognosis. Actually, no single patient in stage II with a lymphoma of high-grade malignancy remained free from disease for more than 12 months after diagnosis. In those with low-grade malignancy only 2 of 16 patients remained disease-free during the observation period. The prognosis in stage II was actually worse than for patients in stages III and IV examined during the same period of time (GLIMELIUS & SUNDSTRÖM). The reason for this may be that systematic chemotherapy was instituted early in patients in stages III and IV. In stage II chemotherapy was not given until later, i.e. at relapse after radiation therapy. In contrast to this poor

outcome for stage II, stage I had a good prognosis irrespective of the histopathologic type, with a 5-year disease-free survival of 60 per cent.

Similar results, with a marked difference in the outcome of stages I and II among patients with high-grade malignancy, have recently been reported by CHEN et coll., who found a 5-year disease-free survival of 79 per cent after radiation therapy in 19 patients in stage I against none of 8 patients in stage II. SWEET et coll. reported on 14 patients in pathologic stage I and 14 in stage II classified as diffuse histocytic lymphomas and given radiation therapy as their primary treatment. Thirteen of the 14 patients in stage I remained disease-free with a median relapse-free survival in excess of 53 months. In contrast, 10 of their 14 patients in stage II had relapsed. The 5-year disease-free survival for stage I patients with high-grade malignancy was in the present series 63 per cent. A similar frequency was reported previously by JONES et coll., BUSH et coll. and CHEN et coll.

In some series 10 to 25 per cent of patients with high-grade malignancy given radiation therapy have developed new disease before the completion of this treatment (KUSHLAN et coll. 1978, LANDBERG et coll. 1979). This was confirmed in the present series, with 8 per cent in stage I and 17 per cent in stage II.

It has been reported that patients in stage I with low-grade malignancy often relapse after local irradiation and that some late relapses may occur after 5 to 10 years (BUSH et coll., ROSENBERG et coll. 1979). In the present series some later relapses occurred but still a 53 per cent relapse-free survival remained after 75 months. Although the observation time may not be entirely sufficient, there seems to be a group of patients who are cured.

Some authors have reported treatment of histopathologically unfavourable NHL of stages I and II with intensive chemotherapy alone (CABANILLAS et coll. 1980) or combined with irradiation (MILLER 1979) with a disease-free survival of 80 to 85 per cent for both stages after a median follow-up period of 27 months. Chemotherapy has been used as adjuvant therapy after irradiation (LANDBERG et coll., MONFARDINI et coll. 1980). The only patients who showed any benefit from this adjuvant therapy were patients in stages I and II with diffuse histocytic or diffuse mixed histopathology (i.e. high-grade malignancy).

Reservation must be made for the examinations for detection of intraabdominal disease, which were not uniformly conducted and were not always sufficiently detailed. The differences in survival in the present report still remained, however, even when the results of lymphangiography, for example, were omitted, or when the patients who were not completely staged were excluded, thus ruling out this factor as a major cause of the observed survival differences.

In conclusion, it was shown that a high proportion of NHL patients in clinical stage I are cured by radiation therapy irrespective of histopathologic type. In contrast, patients in stage II, with very few exceptions, were not cured by radiation therapy alone. The prognosis for patients in stage II in this unselected series was fairly comparable to that in patients in stages III and IV. Primary treatment for stage II with irradiation alone is obviously insufficient for cure, especially in patients with high-grade malignancy who can be cured with intensive chemotherapy (SCHEIN et coll. 1974). Moreover, a high proportion of patients in this group developed progressive disease while receiving radiation therapy. Thus, initial chemotherapy for stage II high-grade malignancies appears to be the treatment of choice. In stage II patients with low-grade malignancy the choice of treatment is more difficult, since chemotherapy has not yet been shown to be curative (PORTLOCK 1980).

SUMMARY

A series of 147 patients, 99 in clinical stage I and 48 in stage II, with localized non-Hodgkin's lymphoma, exclusively given radiation therapy, was retrospectively analysed. Using the Kiel classification, 12 patients (8%) could not be subgrouped with certainty, 63 (43%) were designated as high-grade and 72 (49%) as low-grade malignancies according to the definitions of GÉRARD-MARCHANT et coll. (1974). Complete remission was obtained in 93 per cent of the patients in stage I and in 75 per cent in stage II. Most of the failures (68%) were high-grade malignancies. Actuarial and relapse-free survival was determined for stages I and II and stratified by microscopy and extranodal disease. All patients initially in stage I had a good prognosis irrespective of the microscopic type; 60 per cent have remained free from disease. In contrast, only 2 patients (4%, all low-grade) in stage II have remained disease-free. Thus, in stage II irradiation cannot be considered the best treatment; especially in patients with high-grade malignancy, in whom chemotherapy may be curable. In stage I, on the other hand, irradiation seems to be curative in the majority of patients irrespective of microscopic type.

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